DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 5/17/11 has been entered.

Applicants' Amendment and Response, filed 5/17/11. Claim 41 is cancelled; claim 17 is amended; claims 17, 21-24, 26, 28, 29, 31, 33, 38, and 42 are pending and under current examination.

Information Disclosure Statement

Applicants' IDS, filed 5/17/11, has been considered.

Election/Restrictions

Applicant's election of claims 17-38 (group II), SEQ ID NO:1 and stimulating angiogenesis as the goal of the claimed treatment method in the response on 2/2/2006 is acknowledged. Because Applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor

and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 17, 21, 24, 26, 28, 29, 31, 33, 38, 42 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Alila *et al.* (cited above) in view of Draghia-Akli (cited previously), Fewell et al (cited previously), Gonçalves (**Cardiovascular Res.**, 45: 294-302, 2000), Nicosia *et al.* (**American J. of Pathology**, 145(5): 1023-1029, 1994) and Isner (cited previously).

Applicants' Arguments. Applicants argue that the cited references do not render the claimed invention obvious because none of the cited references refers to a promoter having the sequence of SEQ ID NO: 3. Applicants argue that neither Alila, Draghi-Akli, nor any other cited references, alone or in combination, teach the invention. Specifically SEQ ID NO: 3 is comprised of a 323 bp sequence that can be found in the specification. Draghia-Akli does not teach SEQ ID NO: 3, but discloses a sequence identified and described as a 360 bp Sca1/BamH1 fragment of the SPc5-12 synthetic promoter. Applicants argue that none of Fewell, Goncalves, Nicosia, nor Isner are cited for any teaching to muscle-specific promoters and do not disclose SEQ ID NO: 3. Accordingly, Applicants argue the claimed invention is neither taught nor suggested by the cited references. See pp. 5-6 of the Response.

Response to Arguments. These arguments have been fully considered but are not persuasive. It is noted that Draghia-Akli provide a sequence that is 100% identical to SEQ ID NO: 3. The phrase stating, "the synthetic myogenic promoter having a sequence of SEQ ID NO: 3" (*emphasis added*) is open language; therefore, the sequence of Draghia-Akli continue to anticipate this aspect of the claim, because they teach a promoter sequence that has a sequence of SEQ ID NO: 3. Furthermore, inspection of the instant specification recites that SEQ I DNO: 3 is also known as SPc5-12 (see p. 34 ¶123), which is exactly what is taught by Draghia-Akli. Therefore, one of skill in the art, would readily acknowledge that any differences between the sequence taught by Draghia-Akli, and that of the instant invention are clearly obvious. One of skill in the art would recognize that the promoter taught by Draghia-Akli would provide the same effect as that of the instant claims, namely to drive expression.

Accordingly, the rejection is maintained.

Rejection

Alila *et al.* teach the construction of a plasmid (pIG0552), which contains the 5' portion of the chicken skeletal α-actin gene enhancer/promoter, which is operably linked to the human IGF-I cDNA, and flanked by the 3' portion of human growth hormone UTR (see page 1786, 1st col., 1st ¶ and Figure 1). They teach the purified plasmid was formulated with a complex with PVP (polyvinylpyrrolidone) and then intramuscularly injected into the hind limb of rats (see p. 1787, 1st col., Animal Injections). The muscle samples were then harvested and frozen at various time points and analyzed for hIGF-I expression. Alila *et al.* teach that hIGF-I expression was found localized in the injected muscles (see p. 1790, col. 1-2, bridging ¶). Alila teach intramuscular injection of a construct with a myogenic promoter (chicken skeletal α-actin), which is operably linked to a nucleic acid sequence encoding IGF-I, operably linked to a 3'UTR region, and they teach the expression of this plasmid construct localized to muscle tissue. They teach the limitations of claim 42 because Alila teach the human growth hormone 3'UTR. Alila *et al.* further teach specific embodiments of the claims in that they teach delivery via a single administration (claim 31); delivery into muscle which are diploid cells (claim 33); and that the subject is an animal (rat) (claim 38).

However, Alila *et al.* does not teach a synthetic myogenic promoter that comprises SEQ ID NO:3 (i.e., the synthetic myogenic promoter termed SPc5-12) (claims 17 and 41), nor do they teach a nucleic acid construct comprising an amino acid sequence of SEQ ID NO: 4 (claim 24), or an expression construct that comprises SEQ ID NO: 1 (claim 26) and Alila does not teach transfection enhancing techniques/compounds such as electroporation or transfection facilitating polypeptides as a means to deliver nucleic acids to cells (claims 17, 28, 29).

However, prior to the time of the claimed invention, Draghia-Akli teaches a myogenic promoter consisting of the nucleic acid of SEQ ID NO:3 (i.e. the synthetic myogenic promoter termed SPc5-12). Draghia-Akli teaches a plasmid construct comprising the SPc5-12 promoter operably linked to a nucleic acid encoding human growth hormone releasing hormone (GHRH; page 1182, col. 2, paragr. 3). Draghia-Akli teaches intramuscular injection of said plasmid construct into pigs and then electroporating the injected muscle of said pig to more efficiently deliver said plasmid to the muscle cells (page 1180: col. 1, paragr. 4, line 1 to col. 2, line 10). Thus, Draghia-Akli teaches that said SPc5-12 promoter is a powerful synthetic muscle promoter that drives high level expression of operably linked heterologous nucleic acids in a muscle-specific manner (page 1180, col. 1, lines 1-2).

Fewell teaches intramuscular injection of plasmid DNA complexed with the charge polypeptide poly-L-glutamate into mice followed by electroporation. Fewell

teaches that injection of a plasmid comprising a nucleic acid encoding factor IX and that injection of a plasmid comprising a nucleic acid encoding erythropoietin as such (i.e. forming a complex comprising said plasmids and poly-L-glutamate prior to injection) resulted in enhanced expression of said plasmids compared to when said plasmids were injected as saline solution (i.e. when said plasmids were not complexed with poly-L-glutamate). Thus, Fewell teaches that intramuscular injection of plasmid DNA complexed with poly-L-glutamate followed by electroporation results in more efficient transfection of the cells within the injected muscle.

It would have been obvious to an artisan of ordinary skill at the time of the invention to modify the method of Alila *et al.* with a reasonable expectation of success by: 1) interchanging the avian skeletal chicken skeletal α-actin promoter with the strong muscle-specific synthetic SPc5-12 promoter taught by Draghia-Akli, 2) complexing plasmid DNA with poly-L-glutamate prior to intramuscular injection of said plasmid DNA as taught by Fewell and 3) subjecting muscle tissue injected with said plasmid DNA to electroporation as taught by both Draghia-Akli and Fewell with a reasonable expectation of success. An artisan of ordinary skill would have been motivated to modify the method of Alila as such because: 1) Draghia-Akli teaches that the synthetic SPc5-12 promoter drives high level, muscle-specific expression of operably linked nucleic acids, 2) Fewell teaches that complexing plasmid DNA with poly-L-glutamate prior to intramuscular injection and prior to electroporation results in enhanced uptake of said plasmid DNA and 3) both Draghia-Akli and Fewell teach that electroporating muscle after intramuscular injection of plasmid DNA results in enhanced uptake of said plasmid DNA. Increased cellular uptake of plasmid DNA and increased expression of operably linked nucleic acids contained within said plasmid would be advantageous when practicing methods of gene therapy.

Further, it is noted that pAV2001 (i.e. SEQ ID NO:1 of the instant application) is a hybrid plasmid consisting of fragments of the plasmids taught by Alila (citing Coleman) and Draghia-Akli. The specification on page 42, lines 16-19 recites, "An Nco/HindIII fragment of a SIS II plasmid (Coleman et al., 1995), containing the IGF-I cDNA and the skeletal alpha actin 3'UTR, was cloned into the NcoI/KpnI sites of pSP-HV-GHRH (Draghia-Akli et al., 1999) to generate pSP-IGF-I-SK3'UTR (pAV2001 – SEQID No.: 1)." Thus, an artisan of ordinary skill at the time of the invention would have realized with a reasonable expectation of success that the teachings of Alila (citing Coleman) and Draghia-Akli could be combined to generate the plasmid DNA consisting of the nucleic acid sequence of SEQ ID NO:1.

Although neither Alila, Draghia-Akli or Fewell specifically state that IGF-I is an angiogenic factor, Isner teaches a method for stimulating angiogenesis in an ischemic muscle tissue in a human host comprising injecting into said tissue a DNA sequence encoding an angiogenic protein, wherein said DNA sequence comprises a promoter sequence, wherein the angiogenic protein is selected from a group of angiogenic proteins including insulin-like growth factor (IGF-I; claims 1 and 16; col. 4, lines 8-10, 23). Thus, Isner identifies IGF-I as an angiogenic protein. Additionally, the prior art is replete with teachings to show that IGF-I is an angiogenic factor. Gonçalves teach that state that, "IGF-I has been shown to be an angiogenic growth factor..." See p. 296, col. 2, #3.1, Insulin Growth Factors. They further state that IGF-I seems to participate in inflammation-linked angiogenesis and/or tissue repair (p. 299, col. 1, #4.5, *IGFs and reperfusion.* Similarly, Nicosia *et al.* teach that IGF-I can stimulate rat aortic angiogenesis (see, for example, p. 1024, 1st col., 1st full paragraph). They state that, "Our findings corroborate recent reports that have implicated IGF-I in angiogenesis." See p. 1027, col. 1-2, bridging sentence. Accordingly, one of skill in the art, given the teachings of both Gonçalves and Nicosia would have had a reasonable expectation of success that utilizing a vector containing IGF-I would stimulate or promote angiogenesis.

Accordingly, in view of the combined teachings, it would have been obvious for one of skill in the art to utilize the methods of Alila, to intramuscularly inject a construct that comprises the construct as taught by Alila, Coleman and Draghia-Akli, and to modify this technique by electroporating the muscle after injection of the plasmid DNA, by methods taught by Fewell, with a reasonable expectation of success. One of ordinary skill in the art would have been motivated to make these modifications, as shown above, that Draghia-Akli teach a strong, muscle-specific promoter, and that complexing plasmid DNA with poly-L glutamate prior to intramuscular injection and electroporation after injection results in more efficient transfection of the cells within the injected muscle. The teachings of Isner, Gonçalves and Nicosia provide additional motivation for an artisan of ordinary skill to use a nucleic acid encoding IGF-I to stimulate angiogenesis in muscle and further support that the claimed invention as a whole was *prima facie* obvious.

Claims 22-23 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Alila *et al.* (cited above) in view of Draghia-Akli (cited previously), Fewell et al (cited previously), Gonçalves (**Cardiovascular Res.**, 45: 294-302, 2000, Nicosia *et al.* (**American J. of Pathology**, 145(5): 1023-1029, 1994) and Isner (cited previously) as

applied to claims 17, 21, 24, 26, 28, 29, 31, 33, 38, 42 above, and further in view of van Deutekom *et al.* (Mol. Med. Today, 214-220, May 1998).

Applicants' Arguments. Applicants argue that van Deutekom is not cited for and fails to disclose anything related to SEQ ID NO: 3, and therefore does not remedy the deficiencies listed above.

Response to Arguments. The Examiner has addressed these arguments above. The rejection is proper and is maintained.

Rejection

Alila *et al.*, Draghia-Akli, Fewell, Gonçalves, Nicosia and Isner are summarized above. They do not specifically teach mixing the isolated nucleic acid expression construct with a transfection facilitating system before delivery (claim 22); or that the transfection facilitating system is a liposome or cationic lipid (claim 23). However, prior to the time of the claimed invention, van Deutekom teach that intramuscular injection of non-viral vectors – such as plasmid DNAs – which are encompassed by the instant claims, are shown to have low transfection efficiency, and that these efficiencies can be improved by using non-targeted liposomes and/or polylysine-condensed plasmid DNA (see p. 215, 1st col., 1st ¶, Non-Viral Vectors).

Accordingly, given the combined teachings of Alila *et al.* Draghia-Akli, Fewell, Gonçalves, Nicosia and Isner and van Deutekom, it would have been obvious for one of ordinary skill in the art to modify the method of Alila *et al.*, utilizing a modified vector, as suggested by Draghia-Akli, and utilizing electroporation techniques, taught by Fewell, to mix the isolated nucleic acid expression construct with a transfection-facilitation system, such as utilizing a liposome, as contemplated by van Deutekom, with a reasonable expectation of success. Additionally, one of skill in the art would have had a reasonable expectation of success of stimulating angiogenesis, in view of the teachings of Gonçalves, Nicosia and Isner. One of ordinary skill in the art would have been motivated to make such a modification, as van Deutekom discuss the low transfection efficiency in intramuscular gene delivery, and suggest using non-targeted liposomes to improve efficiency.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Thaian N. Ton whose telephone number is (571)272-0736. The examiner can normally be reached on 9-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Thaian N. Ton/
Primary Examiner, Art Unit 1632